

L2 ANSWER 7 OF 13 MEDLINE
 AN 95147974 MEDLINE
 DN 95147974 PubMed ID: 7845465
 TI **Alzheimer-type neuropathology** in transgenic
 mice overexpressing V717F beta-amyloid precursor protein.
 CM Comment in: Nature. 1995 Feb 9;373(6514):476-7
 Comment in: Nature. 1995 May 25;375(6529):285
 AU Games D; Adams D; Alessandrini R; Barbour R; Berthelette P; Blackwell C;
 Carr T; Clemens J; Donaldson T; Gillespie F; +
 CS Athena Neurosciences, Inc., South San Francisco, California 94080.
 SO NATURE, (1995 Feb 9) 373 (6514) 523-7.
 Journal code: 0410462. ISSN: 0028-0836.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199503
 ED Entered STN: 19950316
 Last Updated on STN: 19980206
 Entered Medline: 19950303
 AB Alzheimer's disease (AD) is the most common cause of progressive
 intellectual failure in aged humans. AD brains contain numerous amyloid
 plaques surrounded by dystrophic neurites, and show profound synaptic
 loss, neurofibrillary tangle formation and gliosis. The amyloid plaques
 are composed of amyloid beta-peptide (A beta), a 40-42-amino-acid fragment
 of the beta-amyloid precursor protein (APP). A primary pathogenic role for
 APP/A beta is suggested by missense mutations in APP that are tightly
 linked to autosomal dominant forms of AD. A major obstacle to elucidating
 and treating AD has been the lack of an animal model. Animals transgenic
 for APP have previously failed to show extensive AD-type neuropathology,
 but we now report the production of transgenic mice that express high
 levels of human mutant APP (with valine at residue 717 substituted by
 phenylalanine) and which progressively develop many of the pathological
 hallmarks of AD, including numerous extracellular thioflavin S-positive A
 beta deposits, neuritic plaques, synaptic loss, astrogliosis and
 microgliosis. These mice support a primary role for APP/A beta in the
 genesis of AD and could provide a preclinical model for testing
 therapeutic drugs.

702 PP

L3 ANSWER 1 OF 1 MEDLINE
 AN 96412254 MEDLINE
 DN 96412254 PubMed ID: 8810256
 TI **Correlative memory deficits, Abeta**
 elevation, and **amyloid plaques** in transgenic mice.
 CM Comment in: Science. 1996 Oct 11;274(5285):177-8
 Comment in: Science. 1997 Aug 8;277(5327):839-41
 AU Hsiao K; Chapman P; Nilsen S; Eckman C; Harigaya Y; Younkin S; Yang F;
 Cole G
 CS Department of Neurology, UMHC Box 295, 420 Delaware Street, University of
 Minnesota, Minneapolis, MN 55455, USA.
 NC AG06656 (NIA)
 AG9009 (NIA)
 NS33249 (NINDS)
 +
 SO SCIENCE, (1996 Oct 4) 274 (5284) 99-102.
 Journal code: 0404511. ISSN: 0036-8075.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199610
 ED Entered STN: 19961106
 Last Updated on STN: 19980206
 Entered Medline: 19961024
 AB Transgenic mice overexpressing the 695-amino acid isoform of human
 Alzheimer beta-amyloid (Abeta) precursor protein containing a Lys670 -->
 Asn, Met671 --> Leu mutation had normal learning and memory in spatial
 reference and alternation tasks at 3 months of age but showed impairment
 by 9 to 10 months of age. A fivefold increase in Abeta(1-40) and a 14-fold
 increase in Abeta(1-42/43) accompanied the appearance of these behavioral
 deficits. Numerous Abeta plaques that stained with Congo red dye were
 present in cortical and limbic structures of mice with elevated amounts of
 Abeta. The correlative appearance of behavioral, biochemical, and
 pathological abnormalities reminiscent of Alzheimer's disease in these
 transgenic mice suggests new opportunities for exploring the
 pathophysiology and neurobiology of this disease.

N 21341193 PubMed ID: 11447836

TI Modelling Alzheimer's disease in multiple **transgenic mice**.

AU Dewachter I; Moechars D; van Dorpe J; Tesseur I; Van den Haute C; Spittaels K; Van Leuven F

CS Experimental Genetics Group, Center for Human Genetics, Flemish Institute for Biotechnology (VIB), K.U. Leuven Campus, Gasthuisberg, B-3000 Leuven, Belgium.

SO BIOCHEMICAL SOCIETY SYMPOSIA, (2001) (67) 203-10.
Journal code: 7506896. ISSN: 0067-8694.

CY England: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200112

ED Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011214

AB We have reported **transgenic mice** with neuronal overexpression of the clinical mutant beta-amyloid precursor protein (APP) known as London, which develop an AD-related phenotype [Moechars, Dewachter, Lorent, Reverse, Baekelandt, Nadiu, Tesseur, Spittaels, Van den Haute, Checler, et al. (1999) J. Biol. Chem. 274, 6483-6492]. Characterized early symptoms (3-9 months) include disturbed behaviour, neophobia, aggression, hypersensitivity to kainic acid, hyposensitivity to N-methyl-D-aspartate, defective cognition and memory, and decreased long-term potentiation. Late in life, at 12-15 months, **amyloid plaques** develop in the brain and correlate with increased levels of beta-amyloid (A beta)40/42 (the 40- and 42-amino-acid forms of A beta). The formation of **amyloid plaques** is dissociated in time from and not involved in the early phenotype. Hyperphosphorylated protein tau is present but no tangle pathology is observed. In double-**transgenic mice**, i.e. APP/London x Presenilin 1, the increased production of A beta 42 results in **amyloid plaques** developing by the age of 6 months. **Transgenic mice** with overexpression of either human apolipoprotein E4 (ApoE4) or human protein tau in central neurons develop severe axonopathy in the brain and spinal cord. Progressive degeneration of nerves and muscles is demonstrated by motor problems, wasting and premature death. Tau is hyperphosphorylated but there is no formation of filaments or **neurofibrillary tangles**. The tangle aspect of AD pathology is still missing from all current transgenic amyloid models. Its implementation will require insight into the cellular signalling pathways which regulate the microtubule-stabilizing function by phosphorylation of neuronal tau.

L4 ANSWER 10 OF 14 MEDLINE
 AN 1999131210 MEDLINE
 DN 99131210 PubMed ID: 9932418
 TI Neurodegenerative Alzheimer-like pathology in PDAPP 717V-->F
transgenic mice.
 AU Chen K S; Masliah E; Grajeda H; Guido T; Huang J; Khan K; Motter R;
 Soriano F; Games D
 CS Athena Neurosciences, South San Francisco, California 94080, USA..
 amyloid!kchen@uunet.uu.net
 SO PROGRESS IN BRAIN RESEARCH, (1998) 117 327-34. Ref: 37
 Journal code: 0376441. ISSN: 0079-6123.
 CY Netherlands
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Priority Journals
 EM 199903
 ED Entered STN: 19990324
 Last Updated on STN: 19990324
 Entered Medline: 19990311
 AB In summary, PDAPP mice overexpressing a mutation associated with some
 cases of familial early-onset AD express several of the major pathological
 hallmarks associated with AD. **Amyloid plaques** in PDAPP
 mice appear quite similar to A beta deposits in AD as shown by a variety
 of different antibodies and stains, and are of both the diffuse and
 compacted varieties. Additionally, a subset of these **amyloid**
plaques appear to be neuritic plaques. Neurodegenerative changes,
 including the loss of synaptic and dendritic proteins, abnormal
 phosphorylation of cytoskeletal elements, subcellular degenerative
 changes, and the deposition of lysosomal and acute phase proteins has also
 been seen in PDAPP mouse brains. Reactive astrocytosis and microgliosis
 have also been observed in association with the **amyloid**
plaques in the PDAPP mice. No **neurofibrillary**
tangles or paired helical filaments have been found in the mice to
 date. It remains unknown whether mice are capable of generating these in a
 manner comparable to AD in less than two years. Extensive behavioral
 analyses are currently being performed in these mice, and preliminary
 results indicate that the PDAPP mice are significantly impaired on a
 variety of different learning and memory tests. In conclusion, the PDAPP
 mouse model doesn't display all the pathological hallmarks of AD, but it
 does display most of them in a robust manner that increases with age and
 gene dosage. Therefore, this transgenic model provides evidence that
 alterations in APP processing and A beta production can result in AD-like
 neuropathology, can contribute to a mechanistic understanding of AD (since
 examination of AD brains yields a static view, and we are unable to view
 the development of various pathological changes), as well as providing an
 useful animal model for the testing of various therapeutic interventions
 directed towards specific aspects of the neurodegenerative process.

L4 ANSWER 9 OF 14 MEDLINE
 AN 2000005421 MEDLINE
 DN 20005421 PubMed ID: 10537029
 TI Progress toward valid transgenic mouse models for Alzheimer's disease.
 AU Guenette S Y; Tanzi R E
 CS Department of Neurology, Massachusetts General Hospital, Charlestown
 02129, USA.. guenette@helix.mgh.harvard.edu
 SO NEUROBIOLOGY OF AGING, (1999 Mar-Apr) 20 (2) 201-11. Ref: 106
 Journal code: 8100437. ISSN: 0197-4580.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Priority Journals
 EM 199912
 ED Entered STN: 20000113
 Last Updated on STN: 20000113
 Entered Medline: 19991229
 AB A transgenic mouse model for Alzheimer's disease (AD) should mimic the
 age-dependent accumulation of beta-**amyloid plaques**,
neurofibrillary tangles, neuronal cell death as well as
 display memory loss and behavioral deficits. Age-dependent accumulation of
 A beta deposits in mouse brain has been achieved in mice overexpressing
 mutant alleles of the amyloid precursor protein (APP). In contrast, mice
 bearing mutant alleles of the presenilin genes show increased production
 of the A beta42 peptide, but do not form amyloid deposits unless mutant
 alleles of APP are also overproduced. Furthermore, the onset of A beta
 deposition is greatly accelerated, paralleling the involvement of
 presenilins in early onset AD. Studies of APP and presenilin
transgenic mice have shown 1) the absence of a
 requirement for a maturation step in dense core plaque formation, 2)
 evidence that beta-amyloid deposition is directed by regional factors, and
 3) behavioral deficits are observed before A beta deposition. Crosses of
 APP **transgenic mice** with mice modified for known AD
 risk factors and "humanizing" the mouse may be necessary for complete
 replication of AD.

L4 ANSWER 12 OF 14 MEDLINE
 AN 95053861 MEDLINE
 DN 95053861 PubMed ID: 7964589
 TI Modeling Alzheimer's disease in **transgenic mice**.
 AU Duff K
 CS Department of Psychiatry, University of South Florida College of Medicine.
 SO JOURNAL OF THE FLORIDA MEDICAL ASSOCIATION, (1994 Sep) 81 (9) 625-8. Ref:
 30
 Journal code: 7505604. ISSN: 0015-4148.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Priority Journals
 EM 199412
 ED Entered STN: 19950110
 Last Updated on STN: 19980206
 Entered Medline: 19941229
 AB Alzheimer's disease is a common neurodegenerative disorder of unknown
 etiology characterized by the accumulation of beta **amyloid**
plaques and **neurofibrillary tangles** in the
 brain. Attempts have been made to engineer an animal model of the disease
 using a variety of transgenic approaches. So far the models have only been
 partially successful. The methods used and the models generated are
 discussed.

L4 ANSWER 14 OF 14 MEDLINE
 AN 92086045 MEDLINE
 DN 92086045 PubMed ID: 1793460
 TI **Amyloid plaques, neurofibrillary**
tangles and neuronal loss in brains of **transgenic**
mice overexpressing a C-terminal fragment of human amyloid
 precursor protein.
 CM Comment in: Nature. 1991 Dec 12;354(6353):432-3
 Retraction in: Kawabata S, Higgins GA, Gordon JW. Nature 1992 Mar
 5;356(6364):23 and Nature 1992 Mar 19;356(6366):265
 AU Kawabata S; Higgins G A; Gordon J W
 CS Department of Geriatrics and Adult Development, Mt Sinai Medical Center,
 New York, New York 10029.
 SO NATURE, (1991 Dec 12) 354 (6353) 476-8.
 Journal code: 0410462. ISSN: 0028-0836.
 CY ENGLAND: United Kingdom
 DT Journal; Article; (JOURNAL ARTICLE)
 (RETRACTED PUBLICATION)
 LA English
 FS Priority Journals
 EM 199201
 ED Entered STN: 19920209
 Last Updated on STN: 19980206
 Entered Medline: 19920121
 AB Alzheimer's disease (AD) affects more than 30% of people over 80 years of
 age. The aetiology and pathogenesis of this progressive dementia is poorly
 understood, but symptomatic disease is associated histopathologically with
amyloid plaques, neurofibrillary
tangles and neuronal loss primarily in the temporal lobe and
 neocortex of the brain. The core of the extracellular plaque is a
 derivative of the amyloid precursor protein (APP), referred to as beta/A4,
 and contains the amino-acid residues 29-42 that are normally embedded in
 the membrane-spanning region of the precursor. The cellular source of APP
 and the relationship of its deposition to the neuropathology of AD is
 unknown. To investigate the relationship between APP overexpression and
 amyloidogenesis, we have developed a vector to drive expression
 specifically in neurons of a C-terminal fragment of APP that contains the
 beta/A4 region, and have used a transgenic mouse system to insert and
 express this construct. We report here that overexpression of this APP
 transgene in neurons is sufficient to produce extracellular dense-core
amyloid plaques, neurofibrillary
tangles and neuronal degeneration similar to that in the AD brain.

L4 ANSWER 12 OF 14 MEDLINE
 AN 95053861 MEDLINE
 DN 95053861 PubMed ID: 7964589
 TI Modeling Alzheimer's disease in **transgenic mice**.
 AU Duff K
 CS Department of Psychiatry, University of South Florida College of Medicine.
 SO JOURNAL OF THE FLORIDA MEDICAL ASSOCIATION, (1994 Sep) 81 (9) 625-8. Ref:
 30
 Journal code: 7505604. ISSN: 0015-4148.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Priority Journals
 EM 199412
 ED Entered STN: 19950110
 Last Updated on STN: 19980206
 Entered Medline: 19941229
 AB Alzheimer's disease is a common neurodegenerative disorder of unknown
 etiology characterized by the accumulation of beta **amyloid**
plaques and **neurofibrillary tangles** in the
 brain. Attempts have been made to engineer an animal model of the disease
 using a variety of transgenic approaches. So far the models have only been
 partially successful. The methods used and the models generated are
 discussed.

L4 ANSWER 13 OF 14 MEDLINE
 AN 92204240 MEDLINE
 DN 92204240 PubMed ID: 1552948
 TI **Amyloid plaques, neurofibrillary**
tangles and neuronal loss in brains of **transgenic**
mice overexpressing a C-terminal fragment of human amyloid
 precursor protein.
 CM Retraction of: Kawabata S, Higgins GA, Gordon JW. Nature 1991 Dec
 12;354(6353):476-8
 AU Kawabata S; Higgins G A; Gordon J W
 SO NATURE, (1992 Mar 19) 356 (6366) 265.
 Journal code: 0410462. ISSN: 0028-0836.
 CY ENGLAND: United Kingdom
 DT (RETRACTION OF PUBLICATION)
 LA English
 FS Priority Journals
 EM 199204
 ED Entered STN: 19920509
 Last Updated on STN: 19920509
 Entered Medline: 19920427

L7 ANSWER 1 OF 7 MEDLINE
 AN 2002366817 IN-PROCESS
 DN 22106566 PubMed ID: 12111445
 TI Potential neurotoxic inflammatory responses to Abeta vaccination in humans.
 AU Munch G; Robinson S R
 CS Neuroimmunological Cell Biology Unit, Interdisciplinary Centre for Clinical Research (IZKF), University of Leipzig, Federal Republic of Germany.
 SO JOURNAL OF NEURAL TRANSMISSION, (2002 Jul) 109 (7-8) 1081-7.
 Journal code: 9702341. ISSN: 0300-9564.
 CY Austria
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS IN-PROCESS; NONINDEXED; Priority Journals
 ED Entered STN: 20020712
 Last Updated on STN: 20020712
 AB SUMMARY: Studies in transgenic mouse models of Alzheimer's disease suggested the development of a vaccine that would induce the production of **antibodies** against **amyloid-beta** (Abeta) peptide, which in turn would stimulate microglia to phagocytose and remove senile plaques. However, some patients in the human **clinical trials** developed symptoms of brain inflammation, demonstrated by lymphocyte infiltration and elevated protein levels. These parameters are indicative of a breakdown of the blood-brain-barrier and entry of T-cells into the brain. Abeta-specific activated T-helper cells have the potential to amplify the existing pro-inflammatory conditions that are present in the brains of Alzheimer's disease patients. Cytotoxic T-cells might even attack the **amyloid** precursor protein which is present on the surface of many cells, including neurons. Before undertaking further vaccination trials there is a need to re-assess the risks associated with Abeta vaccination and with the therapeutic containment of a neuroinflammatory response. These risks may not be justified in the light of recent studies which have shown the efficacy of conventional, low-risk treatments in slowing the progress of AD.

See also Bloss Int. treat Alcy
 NEJM 341(22):1694 J1999